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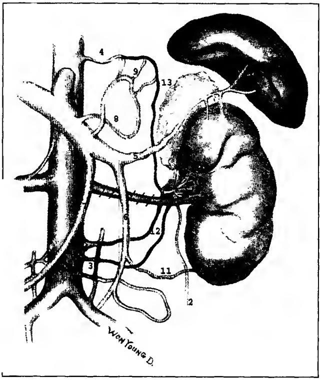

Possible left retroperitoneal collateral pathways for nephrectomy in patient with cirrhosis (page 1094)

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EFFECT OF BASIC FIBROBLAST GROWTH FACTOR INCORPORATING GELATIN MICROSPHERES ON ERECTILE FUNCTION IN THE DIABETIC RAT

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ABSTRACT

Purpose: We report the potential of basic fibroblast growth factor (bFGF) incorporating gelatin microspheres to preserve erectile function in a diabetic rat model.

Materials and Methods: A total of 48 adult male rats were divided into 3 groups, namely control (nondiabetic rats), diabetes mellitus (DM) (diabetic rats that received gelatin microspheres with saline) and bFGF (diabetic rats that received gelatin microspheres with bFGF). After 4 and 8 weeks we examined intracavernous pressure responses with electrical stimulation to the cavernous nerve. For histological examination of the penis we performed Azan-Mallory staining for smooth muscle and collagen, and immunohistochemistry for endothelial nitric oxide synthase (NOS) in endothelium and neuronal NOS in cavernous nerve fiber.

Results: Although the intracavernous pressure response was significantly lower in the DM group than in the control group, pressure in the bFGF group was maintained at the normal level found in controls. Azan-Mallory staining showed a mass decrease in smooth muscle in cavernous tissue in the DM group. However, that in the bFGF group was maintained. There was no significant difference in endothelial NOS positive areas and the distribution of the diameter of neuronal NOS positive nerve fibers in cavernous tissue among the 3 groups.

Conclusions: We report the maintenance of erectile function with bFGF incorporating gelatin microspheres in diabetic rats. The rationale of this maneuver is smooth muscle preservation by the long-term release of bFGF. This is a novel therapeutic option that is clinically applicable for diabetes induced erectile dysfunction.

KEY WORDS: penis, impotence, diabetes mellitus, drug delivery systems, fibroblast growth factor 2

Diabetes mellitus (DM) has been recognized as a major risk factor for erectile dysfunction (ED). The prevalence of ED in men with the disease is almost 3-fold that in the general population.[1] ED is present in 32% of insulin dependent diabetic cases and in 46% of noninsulin dependent diabetic cases.[2] Moreover, patients with diabetes and ED present with worse disease specific quality of life than those with ED but without diabetes.[3] A phosphodiesterase 5 inhibitor is recommended as first line treatment for ED. However, efficacy is significantly lower for diabetic ED than for the nondiabetic type due to tissue damage, including peripheral nerves, endothelium and smooth muscle in the corpus cavernosum.[2]

Cavernous tissue regeneration is a novel approach for the treatment of ED. There have been some experimental successes in ED treatment using growth factors, such as vascular endothelial growth factor,[4] basic fibroblast growth factor (bFGF)[5] and insulin-like growth factor.[6] Since the in vivo half-life of administered growth factor is short, various methods have been used for retaining their activities, such as gene therapy, continuous infusion, repeat injections and sustained release polymers.[5–8]

In the current study we used gelatin microspheres as a carrier because they have demonstrated sustained biological activity with bFGF.[9] In this study we clarified the efficacy of bFGF incorporating gelatin microspheres for diabetic impairment of cavernous tissue.

MATERIALS AND METHODS

Study design. The study was done using 48 adult 10-week-old male Sprague-Dawley rats weighing 300 to 350 gm, which were maintained on a 12-hour daylight cycle with food and water freely available. The animals were divided into 3 groups, namely normal control, DM and bFGF. Control rats received intraperitoneal injection of citrate buffer (100 mM citric acid and 200 mM disodium phosphate, pH 7.0), while DM and bFGF rats received intraperitoneal injection of 60 mg/kg streptozotocin (STZ) dissolved in citrate buffer to induce diabetes. Seven days later animals received intracrural injection of 1 ml of saline (16 controls), microspheres with saline (16 in the DM group) or microspheres with bFGF 20 μg (16 in the bFGF group). The maintenance profile of cavernous tissue was determined 4 and 8 weeks after the injection of citrate buffer or STZ.

Animals were considered diabetic if blood glucose levels were greater than 300 mg/dl. All surgical procedures were performed with the animals under anesthesia with sodium pentobarbital (35 mg/kg). The current experiment was approved by the Animal Experiment Committee of Sapporo Medical University. Animal care, housing and surgery followed the 1988 Guidelines of the Animal Experiment Committee of the University.

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Study received Animal Experiment Committee, Sapporo Medical University approval.
* Correspondence: Department of Urology, Sapporo Medical University School of Medicine, S1-W16, Chuo-ku, Sapporo, Hokkaido, Japan 060-8543 (telephone: 81-(0)11-611-2111, extension 3472; FAX: 81-(0)11-612-2709; e-mail: hisasue@sapmed.ac.jp).

Preparation of bFGF incorporating gelatin microspheres and intracorporeal injection. Gelatin microspheres were prepared through glutaraldehyde (GA) cross-linking of an aqueous gelatin solution, as reported previously.[9] Briefly, the solution was poured into olive oil to form a water in oil emulsion. The emulsion was cooled on ice, washed with acetone and collected by centrifugation. After cross-linking with GA the microspheres were placed in the aqueous glycine solution to block residual GA. The release profile of microspheres in this study was designated as 3 to 4 weeks (20 mg microspheres, 20 ml 0.1% Tween 80 and 500 μl 25% glutaraldehyde).[10] Finally, the average diameter of microspheres was 35 μm (fig. 1). By dropping 4 μl bFGF (10 μg/μl) solution onto 2 mg freeze-dried microspheres bFGF incorporating microspheres were obtained and suspended in 2 ml saline.

After exposure of the penile base and crura a 27 gauge needle with a syringe filled with 0.5 ml of saline or suspended microspheres was gently cannulated in each crus. In the bFGF group the administered bFGF within microspheres was 10 μg per crus (total 20 μg per animal). Following injection the needle was left in place for 5 minutes to allow the microspheres to spread throughout the cavernous space.

Evaluation of erectile function. Erectile function was examined by electrical stimulation of the cavernous nerve in 30 preparations. Systemic mean arterial pressure (MAP) was monitored via a 20 gauge cannula placed in the left carotid artery. A 22 gauge needle was inserted in the penile crus for intracavernous pressure (ICP) measurement. MAP and ICP lines were connected to a pressure transducer, which was connected via a transducer amplifier to a data acquisition board (PowerLab/8sP, ADI Instruments, Milford, Massachusetts). The cavernous nerve was stimulated 3 times per side with a delicate stainless steel bipolar hook electrode (1 mA and 20 Hz for 2 minutes).

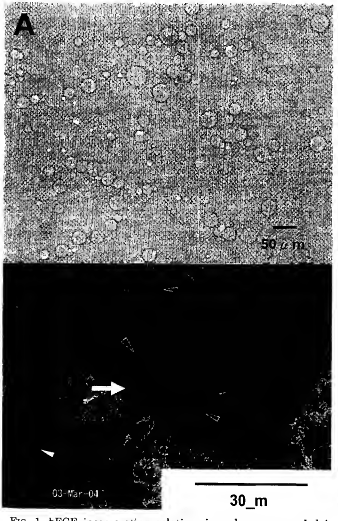

FIG. 1. bFGF incorporating gelatin microspheres suspended in normal saline (*A*). Reduced from ×200. Scanning electron microscopy shows microsphere (white arrow) in cavernous tissue and smooth muscle (black arrows) with some red blood cells (black arrowheads) and collagen fibers (white arrowhead) (*B*). Reduced from ×900.

Histological evaluation. The 18 animals were sacrificed by perfusion fixation with Zamboni's fixative (4% paraformaldehyde containing 0.21% picric acid in 0.1 M. phosphate buffer). The penises were excised. Serial transverse sections were cut at 14 μm on a cryostat.

Smooth muscle and collagen components were quantified via Azan-Mallory staining of cavernous tissue. Immunohistochemical evaluation was done for endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS). Sections were incubated with the primary antibody, mouse anti-eNOS (Transduction Laboratories BD PharMingen, Mississauga, Ontario, Canada) (1:250) or rabbit anti-NOS1 (nNOS) (Santa Cruz Biotechnology, Santa Cruz, California) (1:1,000) and secondary antibodies for each species of biotinylated IgG (Vector Laboratories, Burlingame, California) (1: 500). Following incubation with avidin-biotin complex (Vector Laboratories) (1:100) positive antigens were visualized by incubation with 0.02% 3, 3'-diaminobenzidine tetrahydrochloride. Sections were counterstained with hematoxylin.

Imaging, quantification and statistical analysis. For histological analysis 4 randomly selected fields per animal (12 separate images per group) were studied with a light microscope. To exclude staining artifacts we printed color images, traced only the visible smooth muscle or collagen with tracing paper and scanned and analyzed them using National Institutes of Health (NIH) 1.63 Image Analysis software (NIH, Bethesda, Maryland). The percent positive areas were calculated for smooth muscle, collagen and endothelial cells.

For cavernous nerve analysis 3 penile images per specimen were provided. The diameter of all nNOS positive nerve fibers was measured in the dorsal area and corpus cavernous area of the penile shaft. The distribution of the diameters was divided into less than 2.5, 2.5 to 5 and 5 μm or more.

We used the computer program JMP 5.0.1a (SAS Institute, Cary, North Carolina) for statistical analyses. The ratio of ICP to MAP and the percent positive areas of imaging were compared among the 3 groups by the Dunnett test. The distribution of the diameter of nerve fibers was analyzed by the Kruskal-Wallis test with $p < 0.05$ considered statistically significant. Data are expressed as the mean ± SEM.

RESULTS

Development of diabetes. Table 1 lists blood glucose levels and body weights of control and diabetic rats. Diabetic groups showed an approximately 4-fold increase in the blood glucose concentration and body weight was significantly lower than that of controls. These parameters showed no significant difference between the groups with and without

TABLE 1. *Blood glucose and body weight in each group*

	Mean Initial ± SEM	Mean 4 Wks ± SEM	Mean 8 Wks ± SEM
Blood glucose (mg/dl):			
Control	117 ± 4.4	106 ± 2.7	124 ± 1.6
DM	110 ± 2.6	473 ± 12.7*	475 ± 11.6*
bFGF	120 ± 4.8	451 ± 19.4*	469 ± 12.8*
Wt (gm):			
Control	326 ± 3.7	446 ± 9.3*	528 ± 10.7*
DM	324 ± 1.4	346 ± 7.5	341 ± 11.6
bFGF	324 ± 12.1	341 ± 22.3	357 ± 25.7

Eight animals per group.
* Significantly different vs initial baseline (Dunnet's test $p < 0.05$).

bFGF treatment. Three diabetic rats died of general prostration but there was no death related to microsphere injection.

Functional study. We measured maximal ICP and the ICP-to-MAP ratio during electrostimulation of the cavernous nerve (fig. 2). Electrostimulation in the DM group elicited significantly decreased erectile responses compared with those in the control group (fig. 2, *C*, *D* and *G*). On the other hand, the bFGF group showed significantly higher erectile

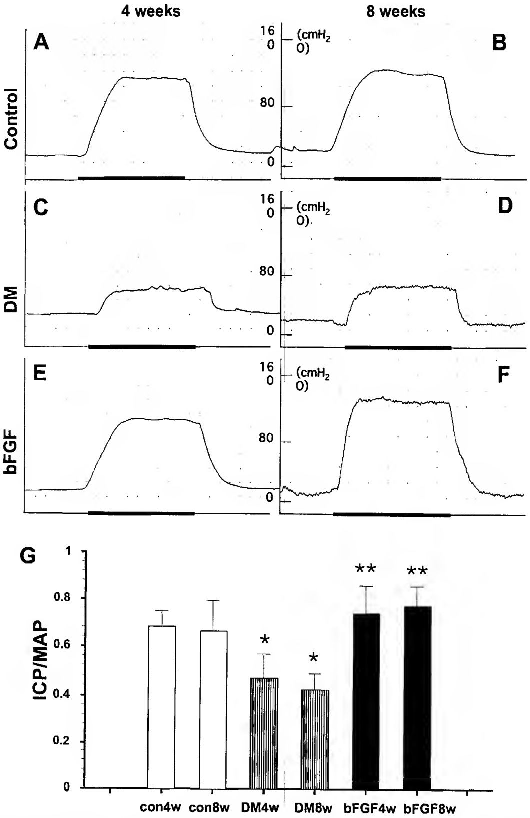

FIG. 2. Representative ICP responses to cavernous nerve electrical stimulation in control group at 4 (*A*) and 8 (*B*) weeks, DM group at 4 (*C*) and 8 (*D*) weeks, and bFGF group at 4 (*E*) and 8 (*F*) weeks. Bold line indicates 2 minutes of electrical stimulation to cavernous nerve. Diagram summarizes ICP/MAP data (*G*). *con4w*, 4-week control. *con8w*, 8-week control. *DM4w*, 4-week DM. *DM8w*, 8-week DM. *bFGF4w*, 4-week bFGF. *bFGF8w*, 8-week bFGF. Single asterisk indicates significantly different vs control (Dunnet's test $p < 0.05$). Double asterisks indicate significantly different vs DM (Dunnet's test $p < 0.05$).

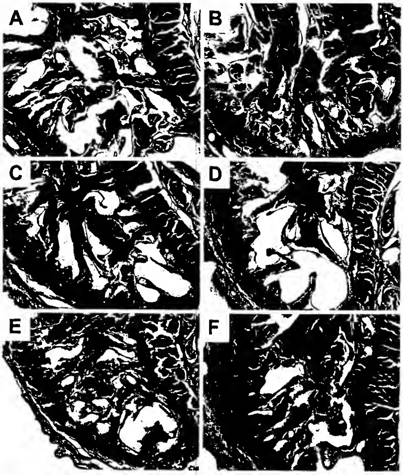

FIG. 3. Penis smooth muscle component stained red and collagen stained blue in control group at 4 (*A*) and 8 (*B*) weeks, DM group at 4 (*C*) and 8 (*D*) weeks, and bFGF group at 4 (*E*) and 8 (*F*) weeks. bFGF group shows smooth muscle cell amount similar to that in control group, while DM group has decreased amount of smooth muscle cells. Azan-Mallory staining, reduced from ×100.

FIG. 4. Immunohistochemical staining of eNOS and nNOS in rat penile shaft uniformly reveal similar locations in corpus cavernosum. eNOS expression (arrows) was localized to endothelial lining of corpora cavernous space in control (*A*), DM (*B*) and bFGF (*C*) groups at 8 weeks. Reduced from ×200. nNOS positive nerve fibers (arrowheads) were observed around small vessels and in smooth muscle in control (*D*), DM (*E*) and bFGF (*F*) group at 8 weeks. Reduced from ×400.

responses than the DM group (fig. 2, *E* to *G*). Moreover, the ICP response in the bFGF group achieved a level as high as that in controls at 4 and 8 weeks (fig. 2, *G*). In a separate series of experiments free bFGF injection did not improve the ICP response, which was similar to that in the DM group without treatments (data not shown).

Azan-Mallory staining. Figure 3 shows representative histochemical results of Azan-Mallory staining. The DM group

TABLE 2. *Area density of smooth muscle cell, collagen and eNOS positive endothelium*

	Mean % 4 Wks ± SEM	Mean % 8 Wks ± SEM
Smooth muscle cell:		
Control	20.3 ± 1.4	19.1 ± 1.1
DM	14.8 ± 1.2*	12.1 ± 1.0*
bFGF	17.4 ± 1.8	17.3 ± 1.2†
Collagen:		
Control	38.6 ± 2.7	36.0 ± 1.7
DM	39.7 ± 3.4	41.8 ± 2.5
bFGF	45.5 ± 2.3	41.7 ± 3.1
Endothelium:		
Control	10.9 ± 0.4	11.0 ± 0.5
DM	10.4 ± 0.5	10.7 ± 0.6
bFGF	10.7 ± 0.5	10.6 ± 0.4

Total of 12 samples per group.

* Significantly different vs control (Dunnet's test $p < 0.05$).

† Significantly different vs DM (Dunnet's test $p < 0.05$).

had a smaller stained area than the control group (fig. 3, *C* and *D*). When areas were quantitatively studied using NIH Image Analysis, the DM group had significantly smaller areas of smooth muscle cells than controls at 4 and 8 weeks (table 2). In contrast, the bFGF group maintained areas comparable to those in normal rats (fig. 3, *E* and *F*). The area of the bFGF group at 8 weeks was significantly larger than that of controls (table 2). With regard to the collagen component there was no significant difference among the 3 groups at 4 and 8 weeks.

Immunohistochemical staining. Immunohistochemical staining showed that eNOS was distributed in the endothelium of cavernous tissue (fig. 4, *A* to *C*). There was no statistically significant difference in eNOS positive area among the 3 groups 4 and 8 weeks after STZ injection (table 2).

Regarding the cavernous nerve, nNOS positive nerve fibers were observed around the small cavernous arteries and in smooth muscles of the corpus cavernosum (fig. 4, *D* to *F*). There was no significant difference in the number of nerves and the distribution of the diameter in the dorsal area or corpus cavernosum among the 3 groups (table 3).

DISCUSSION

Treatment for diabetic ED is a challenging issue.[2] One of the reasons for the low efficacy of ED treatment is considered to be damage to penile vascular structures and cavernous nerves. In diabetic penile tissue sinusoidal endothelial cell denudation, axon degeneration and smooth muscle cell atrophy have been observed.[11] Moreover, diabetic ED is irreversible.[12] Apoptosis of smooth muscle cells leads to veno-occlusive dysfunction, which is refractory to ED treatment other than a penile prosthesis.[13] Therefore, preservation and restoration of the cavernous tissue, including endothelial cells, cavernous nerve and especially smooth muscle, are needed in patients with diabetes to avoid ED.

In vasoreconstruction within cavernous tissue growth factors have been shown to have key roles as novel therapeutic agents in basic studies.[4,5] One of these factors, bFGF, induces angiogenesis that contributes to the pathogenesis of several diseases (ie cancer and atherosclerosis), osteogenesis, adipogenesis and normal wound healing.[14] Moreover, many clinical studies achieved favorable results using recombinant bFGF protein for myocardial angiogenesis.[15] In these studies the therapeutic advantages and safety of bFGF have already been confirmed. In an animal experiment the proliferative effect of systemic bFGF for smooth muscle has been shown in hypercholesterolemic rabbit corporeal tissue.[5] Thus, bFGF is a promising substance as a growth factor to treat ED clinically.

Generally growth factors are unstable in vivo and the application of free forms generates less beneficial biological activities than expected.[16] Recently favorable outcomes were reported in gene therapy with vascular endothelial growth factor in animal models.[4,17] However, there are currently some limitations in such gene therapies, such as toxicity associated with viral vectors or a risk of insertional mutagenesis.[8] In contrast, gelatin microspheres dissolve via gelatin biodegradation in several weeks.[9,10] Biodegradation and the duration of bFGF release can be easily controlled through the cross-linking reaction, which leads to the prolongation of activity. Therefore, bFGF incorporating gelatin microspheres showed higher efficacy than the free form of bFGF for myocardial infarction.[16] Our results indicate that sustained release of bFGF from gelatin microspheres was effective for maintaining smooth muscles. Moreover, the biosafety of gelatin has been proved in various foods and in long-term clinical use. Thus, we believe that the gelatin microsphere is an ideal carrier of bFGF.

The key structure to achieve normal veno-occlusion has been suggested to be the amount of trabecular smooth muscle content in penile corporeal tissue.[18] Our results show that bFGF was effective for maintaining the amount of smooth muscle. Thus, the most rational explanation for the effect of bFGF incorporating microspheres is the preservation of corporeal smooth muscles in type 1 diabetes models. Diabetes related decreases in eNOS protein expression, the percent of endothelial cells and the number of nNOS containing nerve fibers have been reported.[7,19,20] However, in the current study we could not reproduce a histological difference in eNOS and nNOS expression even between the DM and control groups. The current results might have been influenced by the different assessments and designs in previous studies.

To our knowledge the current study is the first to prove that direct injection of bFGF incorporating gelatin microspheres into the corpus cavernosum can preserve erectile function in a diabetic rat model. Although we cannot conclude that bFGF incorporating microspheres can restore severely damaged corpus cavernosum, the current findings indicate that this system has the potential for the regeneration of erectile tissue and it can be useful as a new strategy for ED treatment in the near future.

CONCLUSIONS

The current study indicates that bFGF incorporating gelatin microspheres are effective for the preservation of the

TABLE 3. *Number and diameter of nNOS positive nerve fibers in dorsal area and penile shaft*

	Mean Total ± SEM	Mean Less Than 2.5 μm ± SEM (%)	Mean 2.5–5 μm ± SEM (%)	Mean Greater Than 5 μm (%)
Dorsal area:				
Control	107.0 ± 1.7	64.7 ± 5.8 (60.3)	26.7 ± 3.2 (25.0)	15.7 ± 1.8 (14.7)
DM	112.3 ± 8.2	69.0 ± 9.2 (60.9)	27.7 ± 2.3 (25.0)	15.7 ± 0.3 (14.1)
bFGF	99.3 ± 11.0	61.7 ± 9.0 (61.6)	24.7 ± 2.4 (25.2)	13.0 ± 1.0 (13.2)
Penile shaft:				
Control	25.9 ± 2.6	15.6 ± 1.6 (60.7)	7.7 ± 1.0 (29.8)	2.7 ± 0.8 (9.5)
DM	24.4 ± 2.6	13.7 ± 1.3 (58.1)	7.7 ± 1.0 (30.9)	3.1 ± 1.0 (11.0)
bFGF	22.0 ± 2.0	11.2 ± 1.1 (51.4)	6.8 ± 0.7 (30.9)	4.0 ± 0.8 (17.7)

Nine samples per group with no significant difference among 3 groups by Dunnet's test.

ICP response and corporeal smooth muscles in a diabetic animal model. These results suggest that this modality can potentially be a novel treatment for ED in the future.

Dr. Jintetsu Soh, Kyoto Prefectural University of Medicine, Dr. Kazunori Kato, Seiji Otani, Dr. Ryuichi Kato and Toshie Kurohata, Sapporo Medical University provided technical assistance and M. Kim Barrymore assisted with the manuscript.

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